Vascular disease and the kidney

- **Hypertension**
- **Non-inflammatory renal vessel diseases (thrombotic microangiopathies)**

HTN and the kidney

- **What is HTN? Why is it important?**
- **What causes HTN?**
- **What is the role of the kidney in regulating BP? Which renal diseases cause HTN?**
- **What effects does HTN have on the kidney?**

What is HTN?

What is HTN?

Definition: the level of blood pressure associated with significant morbidity and mortality

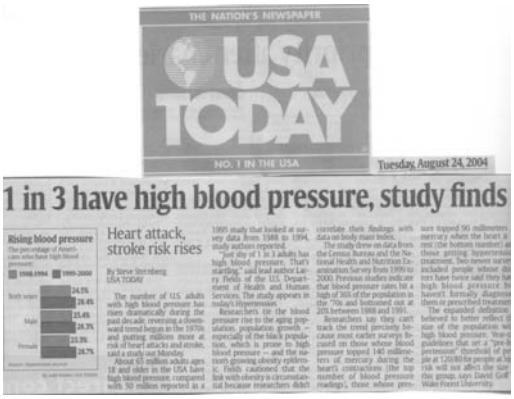
Definition of HTN (DHHS/NIH)

	Diastolic BP		Systolic BP
Normal	<80 mm Hg	And	<120 mm Hg
Pre-hypertension	80-89	Or	120-139
Hypertension stage 1	90-99	Or	140-159
Hypertension stage 2	≥100	Or	≥160

Why is HTN important?

Why is HTN important?

- It's common!
- It's a risk factor for cardiovascular and renal disease
- It's treatable


THE NATION'S NEWSPAPER

USA TODAY

NO. 1 IN THE USA

Tuesday, August 24, 2004

1 in 3 have high blood pressure, study finds

Rising blood pressure

Heart attack, stroke risk rises

By Steve Sternberg
USA TODAY

The number of U.S. adults with high blood pressure has risen dramatically during the past decade, reversing a downward trend begun in the 1970s and putting millions more at risk of heart attacks and stroke, said a study out Monday.

About 65 million adults ages 18 and older in the USA have high blood pressure, compared with 50 million reported in a 1995 study that looked at survey data from 1988 to 1994, study authors reported.

"Just shy of 1 in 3 adults has high blood pressure. That's startling," said lead author Larry Fields of the U.S. Department of Health and Human Services. The study appears in today's Hypertension.

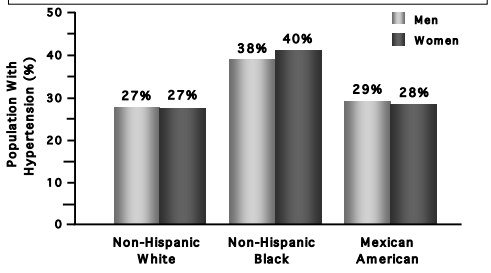
Researchers tie the blood pressure rise to the aging population, population growth — especially of the black population, which is prone to high blood pressure — and the nation's growing obesity epidemic. Fields cautioned that the link with obesity is circumstantial because researchers didn't correlate their findings with data on body mass index.

The study drew on data from the Census Bureau and the National Health and Nutrition Examination Survey from 1999 to 2000. Previous studies indicate that blood pressure rates hit a high of 36% of the population in the '70s and bottomed out at 20% between 1988 and 1991.

Researchers say they can't track the trend precisely because most earlier surveys focused on those whose blood pressure topped 140 millimeters of mercury during the heart's contractions (the top number of blood pressure readings), those whose pressure topped 90 millimeters of mercury when the heart is at rest (the bottom number) and those getting hypertension treatment. Two newer surveys included people whose numbers have twice said they have high blood pressure. Those haven't formally diagnosed them or prescribed treatment.

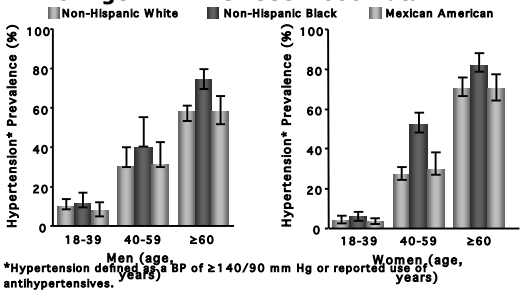
The expanded definition is believed to better reflect the size of the population with high blood pressure. Year's guidelines that set a "pre-hypertension" threshold of people at 120/80 for people at risk will not affect the study, this group, says David Goff, Wake Forest University.

Hypertension Affects Approximately 31% of Adults



Fields LE et al. *Hypertension.* 2004;44:398-404.

Prevalence of Hypertension Increases With Age: NHANES 1999-2000 Data



*Hypertension defined as a BP of ≥140/90 mm Hg or reported use of antihypertensives.

Error bars indicate 95% confidence intervals. Data are weighted to the US population.

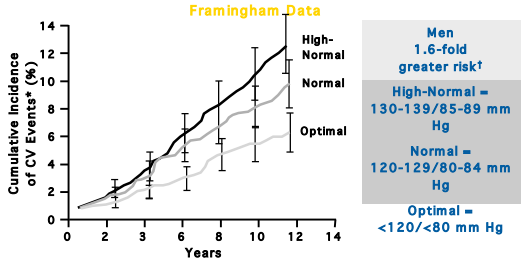
Adapted from Hajjar I, Kotchen TA. *JAMA.* 2003;290:199-206.

Why is HTN important?

B. It's a major risk factor for other disease

- Cardiovascular disease (myocardial infarction, stroke)
- Chronic, irreversible renal failure (end-stage renal disease)

"High-Normal" BP is Not Benign



*CV death, MI, stroke, heart failure. †Adjusted for concomitant CV risk factors.

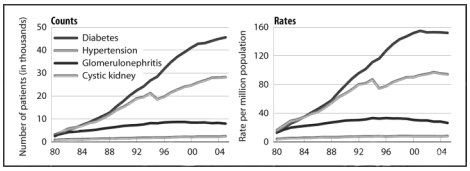
Vasan RS et al. *N Engl J Med.* 2001;345:1291-1297.

Renal manifestations of essential HTN

- Microalbuminuria in up to 37%
- Rarely, heavy proteinuria/nephrotic syndrome
- Elevated creatinine <1%

NB: The high prevalence of HTN makes it the second leading cause (after diabetes) of end-stage renal disease in the U.S.

Incident counts & adjusted rates of ESRD, by primary diagnosis



Incident ESRD patients; rates adjusted for age, gender, & race. Source: USRDS

JNC 7: Lifestyle Modifications to Prevent and Manage Hypertension

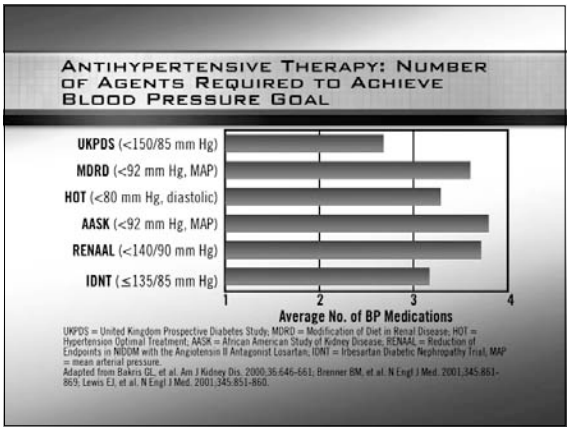
Modification	Approximate SBP reduction
Weight reduction	5-20 mm Hg/10 kg
DASH diet	8-14 mm Hg
Sodium reduction	2-8 mm Hg
Physical activity	4-9 mm Hg
Moderate alcohol consumption	2-4 mm Hg

DASH = Dietary Approaches to Stop Hypertension.
Chobanian AV et al. *JNC 7: Complete Report.*
Available at: http://hyper.ahajournals.org/cgi/content/full/42/6/1206.

Walking the dog

My Doctor said "Only 1 glass of alcohol a day". I can live with that.

1 drink
= 250 ml beer
= 100 ml wine
= 35 ml liquor



What causes HTN?

Primary ("essential") (90-95%)

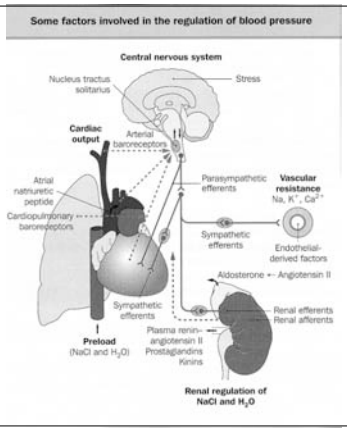
Secondary (5-10%)

- Renal parenchymal disease
- **Renal large vessel disease**
- Pregnancy
- Endocrine disorders, pheochromocytoma
- Coarctation of aorta
- Aortic insufficiency
- Miscellaneous (drugs, neurogenic)

What is the role of the kidney in HTN?

Determinants of blood pressure

BP = Cardiac output x peripheral (arteriolar) resistance



Role of kidney in regulating blood pressure

Regulates total body water/sodium conte

BP = Cardiac output x peripheral resistance

- **Renin-angiotensin systen**
- **Vasodilator substances**

Which kidney diseases cause HTN?

Which kidney diseases cause HTN?

- Most chronic renal parenchymal diseases (e.g. FSGS, IgAN, MPGN)
- **Large renal artery disease (i.e renovascular HTN)**

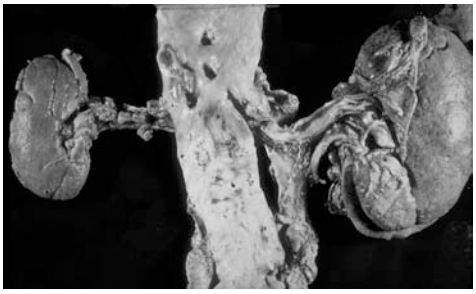
Secondary hypertension due to renal vascular disease

Causes

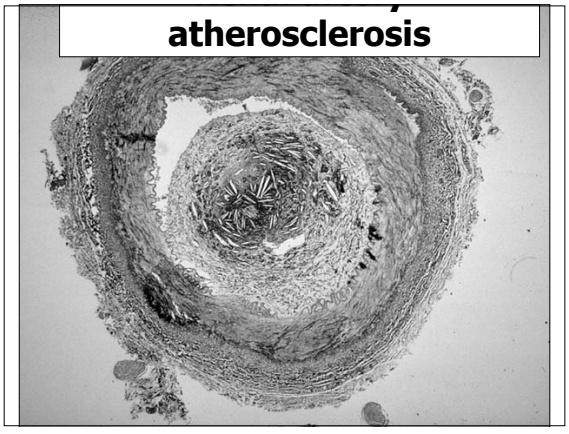
- **Renal artery atherosclerosis**
- **Fibromuscular dysplasia**
- Congenital anomalies
- Takayasu's aortitis
- Radiation
- Tumor
- Post-op stricture

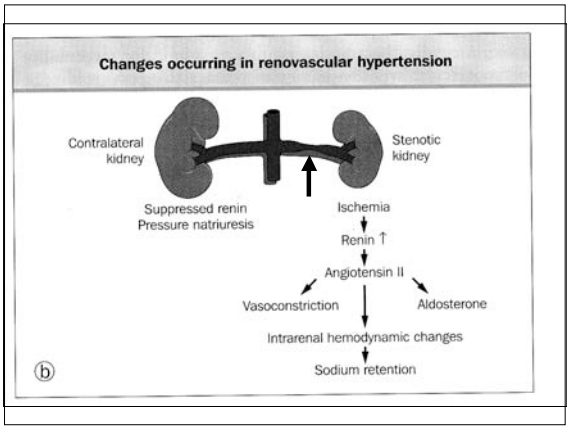
Renal artery stenosis

Renal artery atherosclerosis



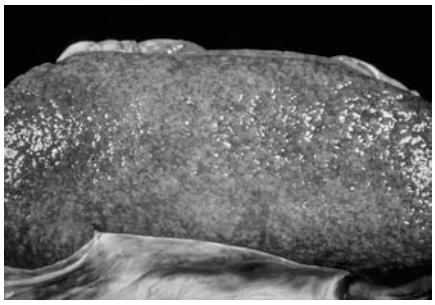
atherosclerosis



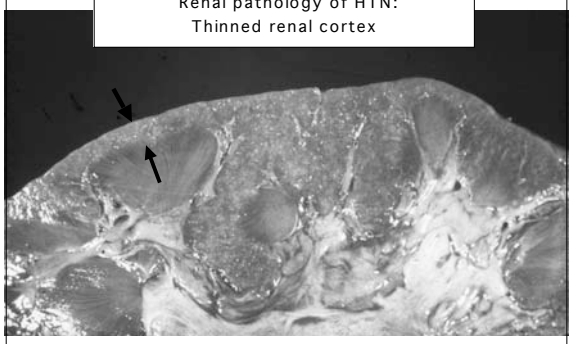


What effects does HTN have on the kidney?

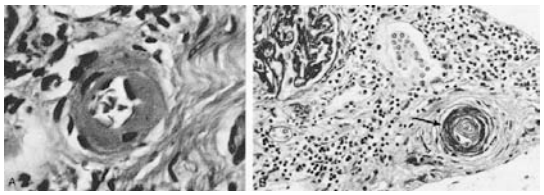
Renal pathology of HTN:
Granular surface



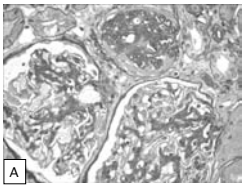
Renal pathology of HTN:
Thinned renal cortex

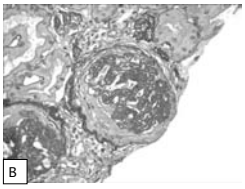


Hypertensive arteriolosclerosis

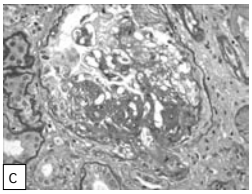


Arteriolar sclerosis and hyalinosis





Arterionephrosclerosis-
- Glomerulomegaly
- Global sclerosis
- Perihilar FSGS



Renal pathology of HTN: arterionephroclerosis

Gross:
shrunken, finely granular kidneys

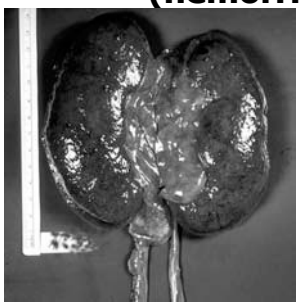
Micro:
1. Arteriolosclerosis
2. Secondary glomerulosclerosis (FSGS and global sclerosis)
3. Tubular atrophy and interstitial fibrosis

Q: In unilateral renal artery stenosis, which kidney is more likely to show hypertensive nephrosclerosis?

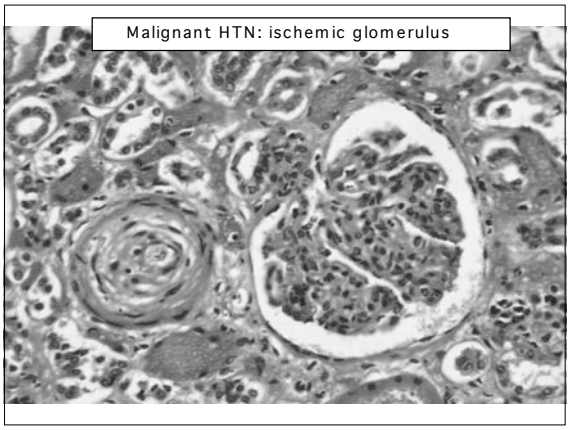
Renal disease caused by HTN

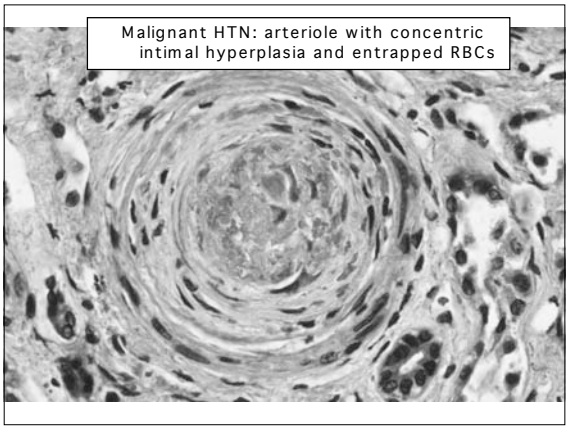
- **Essential HTN**
  - **<1% develop ESRD**
  - **A small no. develop proteinuria**
- **Accelerated (malignant) HTN**
  - **Acute renal failure in most**
  - **Hemolytic anemia**
  - **Headache, Stroke, retinal damage**
  - **50% mortality is untreated**

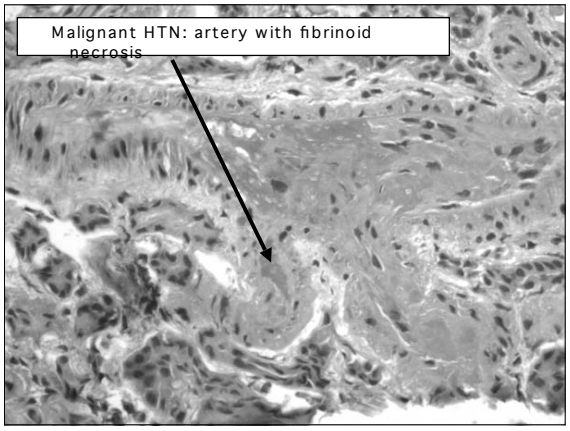
Malignant HTN: "flea-bitten" kidney (hemorrhages)

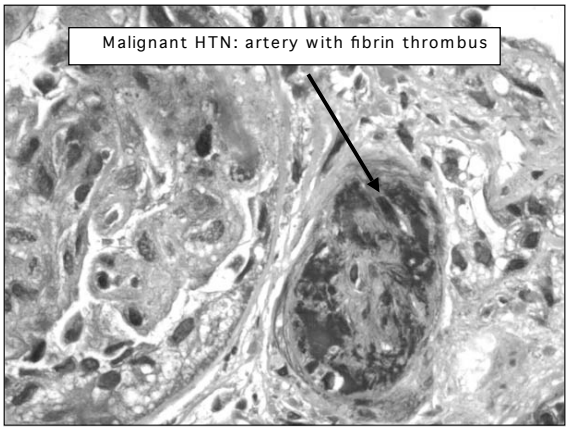


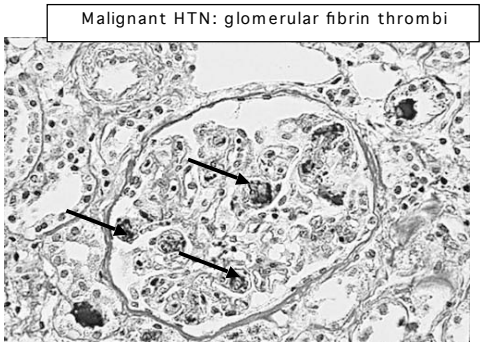
- **Petechial hemorrhages**
- **Capsule may be smooth if de novo (90%)**
- **Granular if previous HTN (10%)**



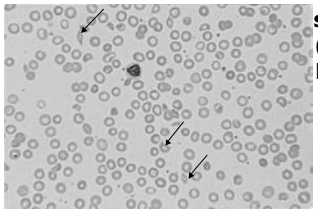








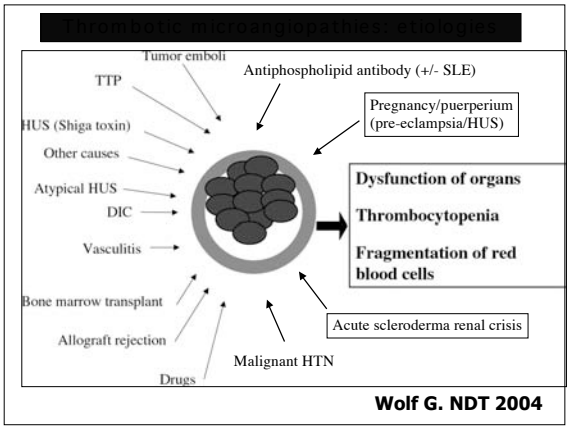
Peripheral blood smear in malignant HTN

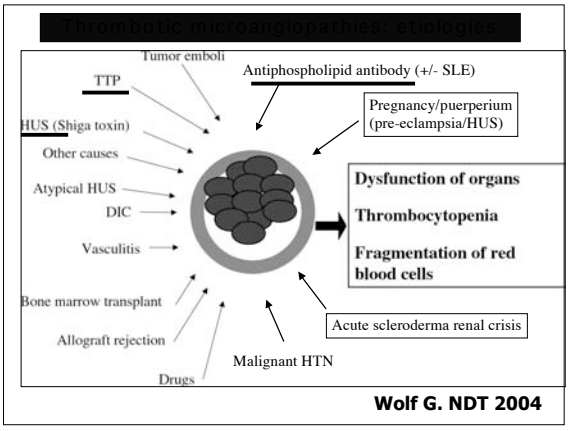


schistocytes (fragmented RBCS)

arterioles/capillaries (Thrombotic microangiopathy)

- Hemolytic anemia
- Thrombocytopenia
- Acute renal failure





Case

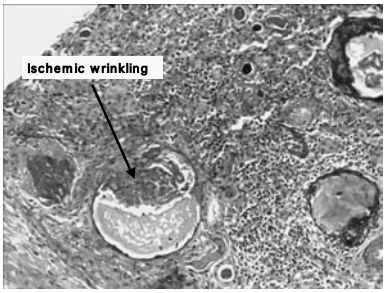
- **45 yo WF admitted for skin rash and ARF**
- **History of 3 spontanous abortions**
- **BP 170/84, UE and LE rash; Chest neg, no edema.**
- **BUN 97 mg/dl Creatinine 4.0 mg/dl Palb 3.5**
- **WBC 11.2K Hct 37% plts 114 K , Pt 14 PTT 49 U/A 1+ prot +rbc no casts**
- **ANA + 1: 40; Hep BV,HCV neg, HIV-, ANCA – , CH50 and C3 nl**
- **Anticardiolipin antibody strong positive**

Antiphospholipid Antibodies

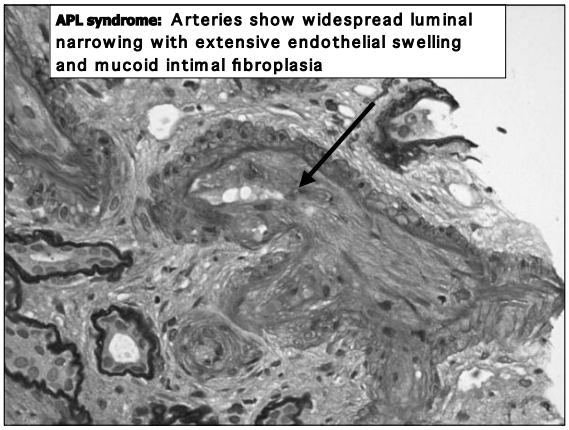
- Family of Antibodies (IgG, IgM, IgA) aganist negatively charged phospholipids
- Lupus Anticoagulant - Abs that prolong lipid dependent coag tests, interfere with phospholipid of the prothrombin activator complex.
- Anticardiolipin antibodies - Abs that bind to cardiolipin (phospholipid antigen used in tests for syphilis)
- False + VDRL
- Procoagulant Effect in vivo

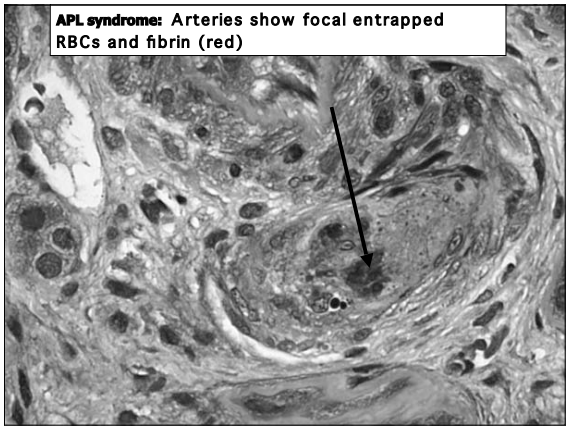
Underlying Conditions with Antiphospholipid Antibodies

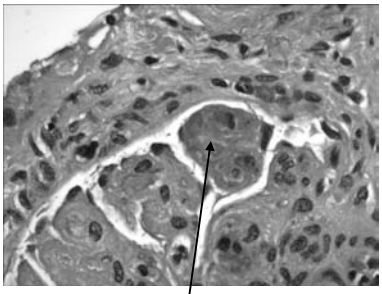
- Systemic Lupus Erythematosus
- "Lupus-Like" Syndrome
- Primary Anti-phospholipid Syndrome



APL syndrome: Glomeruli show ischemic changes (global wrinkling of glomerular basement membranes, tuft retraction, and cystic dilation of Bowman's space)







APL syndrome: Glomerulus shows segmental intracapillary fibrin

Diagnosis

- **Primary antiphospholipid antibody syndrome with features of arteriolar and glomerular thromboses**

Clinical Manifestations Related to Anticardiolipin Antibodies

- Recurrent arterial and venous thromboses
- Placental thromboses and spontaneous abortions
- Livedo reticularis
- CNS complications
- Pulmonary Hypertension

Case

- **A 4 yo girl presents with diarrhea and acute renal failure.**
- **She was in good health until 3 days PTA when went to neighbor's Bar-B-Q and had a hamburger. Over 24 hrs developed abdominal cramps, N/V, and bloody diarrhea. She became lethargic took in less fluids and her parents brought her to ER.**
- **BP 70/45 mm Hg, P130 /min, T 101, Cor-Chest -, Abd diffuse mild tender , increased BS, ext- no edema, + petechiae on legs.**
- **WBC 12.2K, Hct 28%, plts 52K, smear with schistocytes.**
- **BUN 45 mg/dl, creatinine 3.1 mg/dl.**
- **U/A 2+ prot. 3+ heme, +rbc TNTC, + rbc casts.**

From the Centers for Disease Control and Prevention

Leads From the Morbidity and Mortality Weekly Report
Atlanta, Ga 3-3-93

Preliminary Report: Foodborne Outbreak of *Escherichia coli* O157:H7 Infections From Hamburgers—Western United States, 1993

Multi-State Outbreak of *E. coli* O157:H7 Infections From Fresh Spinach, October 6, 2006

- 199 persons infected with the outbreak strain of *E. coli* O157:H7 reported to CDC from 26 states.

Childhood HUS

- E. coli shigatoxin-associated
- 2.1per 100,000 /yr (peak < 5 yo)
- Warm summer months
- Onset GI sx, cramps, diarrhea, n/v, fever
- 70% bloody diarrhea w/i 2 days
- 5-10% develop renal involvement

Role of Shiga Toxin

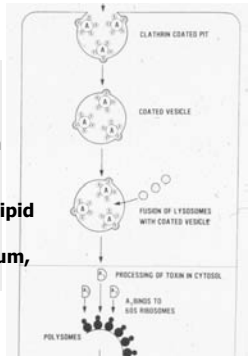
- Epidemic and sporadic HUS
- E. Coli 0157:H7 produce both STX1 and STX2
- Causes Hem. Colitis & is cytopathic to green monkey kidney cells
- STx – E coli in stool for wks

Transmission of E. Coli - STX

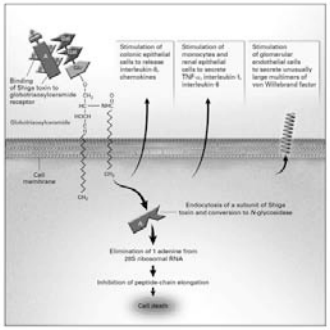
- E. coli in cattle (& other animals) – manure, water troughs, farms
- Transmit by food or water
- Usually beef contaminated at slaughter
- Also raw milk, fruit & veg, apple cider, apple juice, spinach
- Person to person – day care centers

Verotoxin

- **A subunit binds 60S Ribosomes, inhibit protein synthesis**
- **5 B subunits binds glycolipid receptors (gb3) on surface of colonic epithelium, endothelium, and WBCs**



Shiga Toxin and Cell Injury



Moake, NEJM 2002

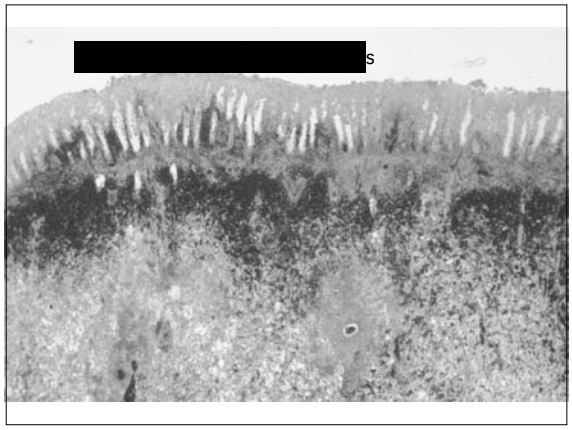
Shigatoxin-1 and Endothelium

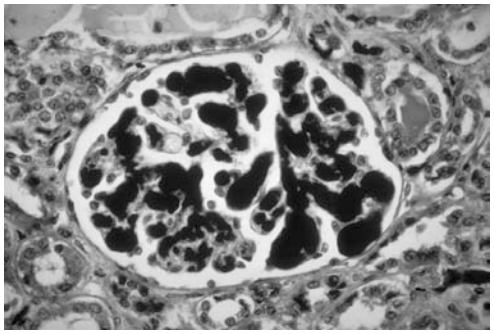
- **Binds to Gb3 on glomerular endothelium**
- **Gb3 expression equal in children vs. adults**
- **Mechanism for childhood susceptibility remains undetermined**

Ergonul, et al, 2003

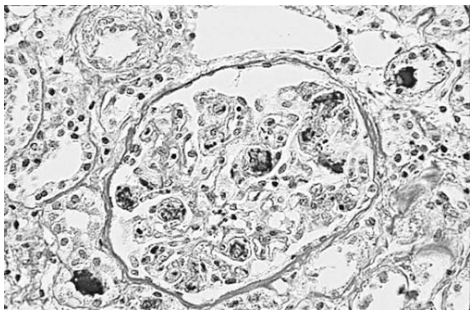
Case 4: E.coli-associated HUS

- **Pathologic findings**

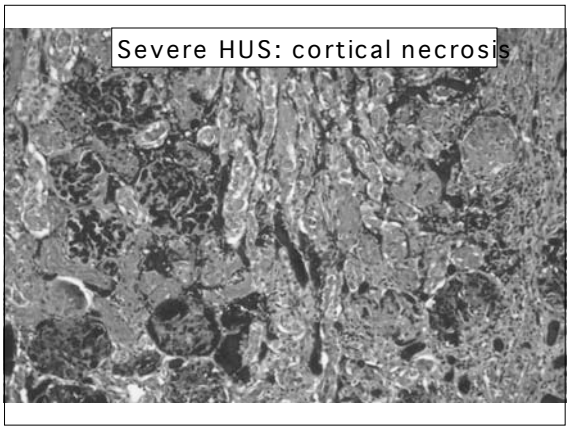




Fibrin thrombi in TMA



thrombi in glomerular capillaries



Course ARF Childhood HUS

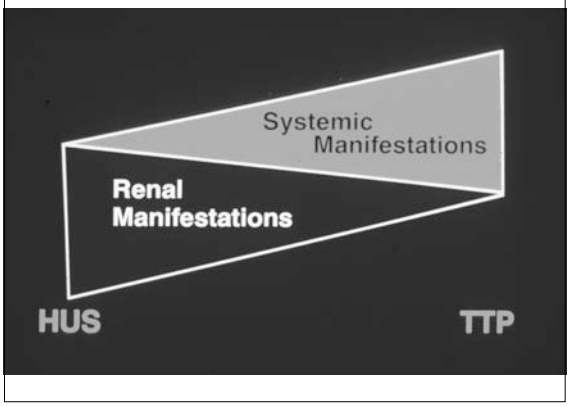
- **50% dialysis**
- **75% transfusions**
- **25% Neuro sx (CVA, sz, coma)**
- **3-5% die in acute phase**
- **Long term renal dysfunction is common**

Higher Risk HUS

- **Antibiotics**
- **Bloody diarrhea**
- **Fever, vomiting**
- **Leukocytosis**
- **< 5 yo**
- **females**

Residual Renal Disease in Childhood HUS

- **3-18% ESRD**
- **10-40% low GFR, proteinuria, CRF, HBP**
- **Duration of anuria predicts poor renal outcome**
  - **< 10 days → 7.5%**
  - **> 16 days → 42.5%**



Thrombotic thrombocytopenic purpura (TTP)

- CNS signs predominate
- Deficiencies of vWF cleaving metalloproteinase (ADAMTS13)
  - Hereditary (rare)
  - Acquired (autoantibodies)